Early Developmental Outcome in Children With Hypoplastic Left Heart Syndrome and Related Anomalies

The Single Ventricle Reconstruction Trial

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Background—Survivors of the Norwood procedure may experience neurodevelopmental impairment. Clinical trials to improve outcomes have focused primarily on methods of vital organ support during cardiopulmonary bypass.

Methods and Results—In the Single Ventricle Reconstruction trial of the Norwood procedure with modified Blalock-Taussig shunt versus right-ventricle-to-pulmonary-artery shunt, 14-month neurodevelopmental outcome was assessed by use of the Psychomotor Development Index (PDI) and Mental Development Index (MDI) of the Bayley Scales of Infant Development-II. We used multivariable regression to identify risk factors for adverse outcome. Among 373 transplant-free survivors, 321 (86%) returned at age 14.3±1.1 (mean±SD) months. Mean PDI (74±19) and MDI (89±18) scores were lower than normative means (each $P<0.001$). Neither PDI nor MDI score was associated with type of Norwood shunt. Independent predictors of lower PDI score ($R^2=26\%$) were clinical center ($P=0.003$), birth weight <2.5 kg ($P=0.023$), longer Norwood hospitalization ($P<0.001$), and more complications between Norwood procedure discharge and age 12 months ($P<0.001$). Independent risk factors for lower MDI score ($R^2=34\%$) included center ($P<0.001$), birth weight <2.5 kg ($P=0.04$), genetic syndrome/anomalies ($P=0.04$), lower maternal education ($P=0.04$), longer mechanical ventilation after the Norwood procedure ($P<0.001$), and more complications after Norwood discharge to age 12 months ($P<0.001$). We found no significant relationship of PDI or MDI score to perfusion type, other aspects of vital organ support (eg, hematocrit, pH strategy), or cardiac anatomy.

Conclusions—Neurodevelopmental impairment in Norwood survivors is more highly associated with innate patient factors and overall morbidity in the first year than with intraoperative management strategies. Improved outcomes are likely to require interventions that occur outside the operating room.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00115934.

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Key Words: cardiac surgery ■ congenital cardiac defects ■ congenital heart disease ■ heart defects, congenital ■ hypoplastic left heart syndrome

Survival to adulthood is becoming a reality for patients with hypoplastic left heart syndrome (HLHS) and other single right ventricle anomalies treated with staged repair from the Norwood operation to the Fontan procedure. This remarkable progress has exposed a high prevalence of neurodevelopmental impairment in survivors,[1–5] affecting their educational achievement, employability, and quality of life.[6,7] Potential risk factors for adverse neurodevelopmental out-

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come in this population include patient and environmental factors,[8–12] management practices,[13–22] and medical course.[23,24]

Clinical Perspective on p 2091

The Single Ventricle Reconstruction (SVR) trial compared outcomes in subjects with HLHS or related anomalies palliated by using the Norwood procedure with either a modified Blalock-Taussig (MBT) shunt or the right-ventricular-to-pulmonary-artery (RV-to-PA) shunt. The primary outcome was freedom from death or cardiac transplantation by 12 months postrandomization.[25] In this article, we report an important prespecified secondary trial outcome, neurodevelopment assessed by in-person evaluation at 14 months after randomization. We evaluated the influence of shunt type on neurodevelopmental outcome based on the hypothesis that the RV-to-PA shunt group would have better neurodevelopment because of its potential advantage of reducing the aortic diastolic runoff and hence improving cerebral blood supply in the early postoperative period. As a secondary analysis, multivariable regression was used to identify other risk factors for adverse neurodevelopmental outcome. The SVR trial is the largest prospective study of children undergoing the Norwood procedure. Developmental testing at age 14 months in this cohort provides an unparalleled opportunity to explore the correlates of neurodevelopment and to identify potential modifiable risk factors.

Methods

Subjects

Details of the SVR trial design have been published.[26] Patients were recruited from 15 centers in North America participating in the National Heart, Lung, and Blood Institute-funded Pediatric Heart Network between May 2005 and July 2008. Inclusion criteria consisted of a diagnosis of HLHS or other single, morphological right ventricle anomaly and planned Norwood procedure. Exclusion criteria included preoperative identification of anatomy rendering either a MBT shunt or a RV-to-PA shunt technically impossible and any major congenital or acquired extracardiac abnormality that could independently affect the likelihood of the subject meeting the primary outcome of transplant-free survival at 12 months postrandomization. The protocol was approved by the institutional review board at each center, and written informed consent was obtained from a parent/guardian before randomization.

Neurodevelopmental Assessment

The primary measure of neurodevelopment was the Bayley Scales of Infant Development-Second Edition (BSID-II).[27] Every examiner participated in conference calls in which the study protocol, the certification process, and data-reporting procedures were discussed. Each submitted 2 videotaped assessments of children similar in age to trial subjects to be certified by a single expert (D.C.B.) before administering the BSID-II to a trial subject. These tapes, and the associated examiner record forms, were reviewed to ensure that appropriate administration and scoring procedures were followed. Throughout the study, the examiner record form for each trial subject was reviewed by D.C.B. for completeness and accuracy. The BSID-II was only administered in English or Spanish, and it was administered in the dominant language spoken in the home. Testing personnel were blinded to the treatment assignment of the subjects.

The BSID-II offers a standardized assessment of cognitive and motor development for children aged 1 through 42 months.[27] It yields 2 scores: the Psychomotor Development Index (PDI) and the Mental Development Index (MDI). The mean±SD for PDI and MDI scores in the normative population is 100±15.

Study Design and Measurements

Subjects were randomly assigned to either a MBT shunt or a RV-to-PA shunt within strata defined by the presence or absence of aortic atresia and of obstructed pulmonary venous return, with dynamic balancing within surgeon. In all other respects, they were managed according to the usual practices at their clinical centers. A complete list of variables that were recorded and analyzed is provided in online-only Data Supplement Table I. In brief, before the Norwood procedure, we recorded demographic and preoperative medical history, including pregnancy history, fetal diagnosis, birth weight, race, sex, gestational age, Apgar scores, clinical status and anatomic diagnosis at presentation, occurrence of important preoperative complications, and age at operation.[26] We recorded intraoperative variables at the time of the Norwood procedure, the stage II procedure, and any additional cardiac operations, including total support time, total bypass time, and durations of deep hypothermic circulatory arrest (DHCA) and regional cerebral perfusion (RCP) times; details of bypass (eg, lowest temperature, use of modified ultrafiltration, use of α-blockade); and shunt type. The perfusion method during vital organ support was classified as DHCA, RCP, or DHCA+RCP. Patients who received RCP with ≤10 minutes of DHCA, usually to allow for repositioning of cannulae, were classified in the RCP group. Shunt type was defined as the shunt in place at the end of the Norwood procedure, which differed from the randomly assigned shunt for 22 (7%) subjects with a Bayley score. Postoperative data during the admissions for the Norwood and stage II operations were prospectively collected by daily review and included procedures and events. Twelve months after randomization, we recorded vital status and interim medical history. At the in-person evaluation 14 months after randomization, we performed neurodevelopmental testing and collected data on height, weight, head circumference, interim medical history, and socioeconomic status. In addition to genetic evaluations performed during routine clinical care, an optional research genetic evaluation was offered to families. Patients were classified with regard to whether they had (1) a specific genetic syndrome or (2) other anomalies (ie, not identified with a syndrome). Growth data were converted into age-adjusted z scores based on World Health Organization standards.[28]

Statistical Methods

Descriptive statistics include median with interquartile range for skewed variables, mean± SD for other continuous variables, and frequency with percentage for categorical variables. The frequency distributions of duration of mechanical ventilation and hospital stay were nonlinearly related to outcome; thus, we used a natural logarithmic transformation. We used median imputation for highest lactate level with values specific to preintubation status (101 subjects) and mean imputation for Apgar scores (20 subjects). For the Bayley scores, interactions between each candidate predictor and 4 prespecified variables were examined: (1) birth weight <2.5 kg versus ≥2.5 kg; (2) gestational age <37 weeks versus ≥37 weeks; (3) pre-Norwood head circumference z score <−1 versus ≥−1; and (4) presence versus absence versus unknown status of a genetic syndrome or other abnormality. We used simple linear regression and regressions adjusted for site to obtain initial estimates of association of each candidate predictor with PDI and MDI scores. All variables with unadjusted $P<0.20$ were used as candidate predictors for multivariable modeling. Interaction terms were allowed to enter the multivariable model only in hierarchical fashion. Stepwise linear regression was used to develop multivariable models, in conjunction with bootstrapping (1000 samples) to obtain reliability estimates for each of the predictors. We required that all terms in the final multivariable

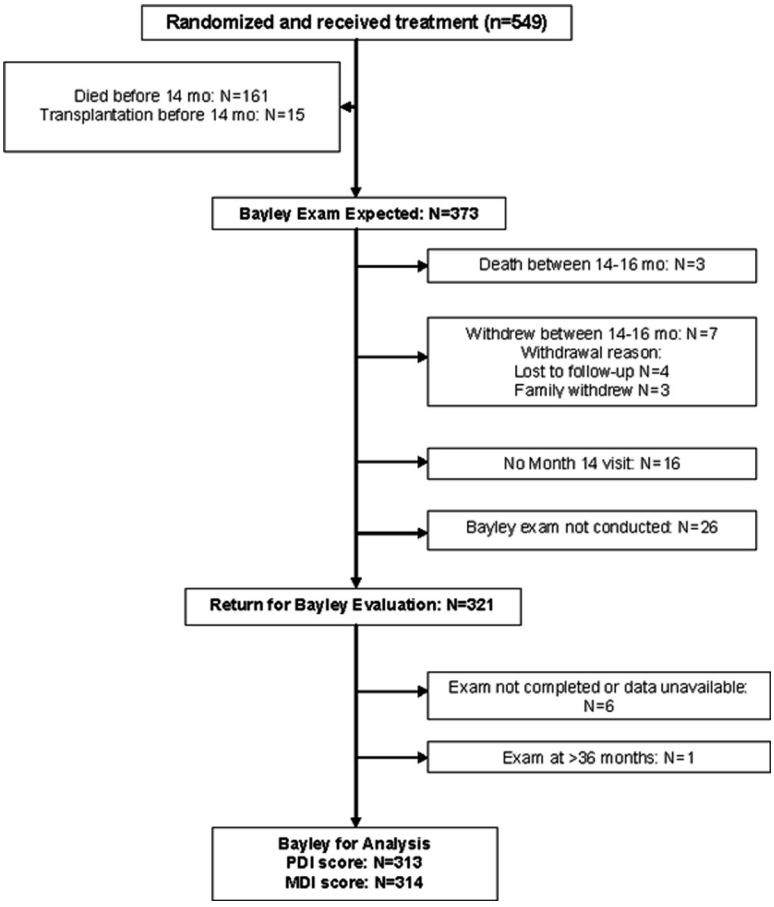

Figure 1. Flow chart of SVR trial subjects from randomization to neurodevelopmental follow-up. SVR indicates Single Ventricle Reconstruction.

model have a reliability >50% and $P<0.05$. All analyses were conducted using SAS version 9.2 (Statistical Analysis System, SAS Institute, Inc., Cary, NC) and SAS macros for bootstrapping estimates of reliability.

Results

A flow chart of SVR trial subjects from randomization to neurodevelopmental follow-up is shown in Figure 1. The follow-up rate for the BSID-II examination among transplant-free survivors was 86%. The mean (±SD) age at follow-up was 14.3±1.1 month (range, 12.2–19.5 months). The 314 patients who completed the examination were less likely to be of black or other race ($P<0.001$). However, the groups did not differ in their socioeconomic class or level of highest maternal education. The mean time interval between the Norwood and stage II procedures was 5.2±1.9 months (median, 5.0 months). Ten (3%) subjects in the cohort were not discharged between stage I and II surgery.

At 14 months, children had impaired growth: mean weight, height, and head circumference z scores for age were −0.7±1.1, −1.3±1.7, and −0.4±1.4, respectively. Among the 296 subjects for whom a parent history was available, 47% had received developmental support in the first year of life: 39% with physical therapy, 26% with speech/language therapy, 10% with early intervention, and 4% with other forms of support. Genetic syndromes or other anomalies were detected in 25% of the cohort and were absent in 57%; the remaining 18% were not evaluated by a geneticist. Subjects with confirmed genetic syndrome and other anomalies had longer hospitalization (median, 28 days [interquartile range, 20–43 days] versus 22 days [interquartile range, 16–35 days] and 24 days [interquartile range, 17–38 days] for no and unknown syndrome status, $P=0.01$). Birth weight tended to be lower in the patients with confirmed genetic syndromes (3.0±0.6 versus 3.2±0.5 or 3.2±0.5 kg in the no and unknown groups, $P=0.06$). Among patients returning for neurodevelopmental testing, the 2 shunt groups were comparable with respect to birth characteristics (eg, gestational age and birth weight), demographic and socioeconomic factors, anatomy, and the proportion with a genetic syndrome or other anomalies.

Distributions of PDI and MDI scores are depicted in Figure 2. Tables 1 and 2 summarize the significant univariate associations ($P\leq0.05$) of PDI or MDI score with patient factors, management practices, and medical course.

For the overall cohort, PDI scores were profoundly lower than in the normative population (Figure 2): scores were <85 (>1 SD below expected mean) in 65% of subjects, and <70 (>2 SD below expected mean) in 44% of subjects. Subjects who received the MBT shunt and RV-to-PA shunt had similar PDI scores (75±19 versus 74±20, respectively, $P=0.48$; see online-only Data Supplement Figure I). The subgroup of subjects with no genetic syndrome and birth weight of ≥2.5 kg had the highest PDI and MDI scores (each $P<0.001$) and also had shorter Norwood hospital length of stay ($P=0.033$). In multivariable linear regression modeling (Table 3), inde-

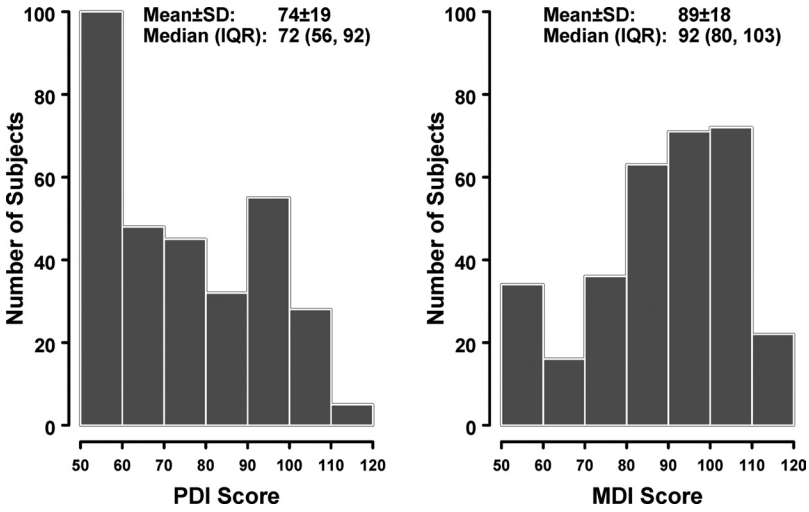

Figure 2. Histogram depicting the number of subjects according to scores on the Psychomotor Development Index (PDI, **left**) and Mental Development Index (MDI, **right**) of the Bayley Scales of Infant Development-Second Edition. IQR indicates interquartile range.

pendent predictors of lower PDI scores were clinical center where the Norwood procedure was performed ($P=0.003$), birth weight <2.5 kg ($P=0.02$), longer log-transformed days of Norwood hospitalization ($P<0.001$), and greater number of complications between the time of discharge after the Norwood procedure and age 12 months ($P<0.001$). The percentage of variance explained by the model (adjusted R^2) was 26%. Mean PDI score dropped ≈13 points for every 3 extra days of hospital stay during the Norwood hospitalization. Presence of a genetic syndrome or other anomaly did not achieve statistical significance ($P=0.07$).

MDI scores were also much lower than in the normative population (Figure 2): scores were <85 (>1 SD below normal mean) in 36% of subjects and <70 (>2 SD below normal mean) in 16% of subjects. Within subject, MDI scores were higher than PDI scores ($P<0.001$). Mean MDI scores did not differ significantly between patients who received the MBT shunt versus the RV-to-PA shunt (89±17 versus 88±18, respectively, $P=0.55$; online-only Data Supplement Figure I). In multivariable regression analysis (Table 3), independent predictors of lower MDI score included the clinical center where the Norwood procedure was performed ($P<0.001$), birth weight <2.5 kg ($P=0.04$), the presence of a genetic syndrome or other anomalies ($P=0.04$), lower maternal education level ($P=0.04$), longer log days on the ventilator after the Norwood procedure ($P<0.001$), and a greater number of complications between the time of hospital discharge after the Norwood procedure and age 12 months ($P<0.001$). The percentage of variance explained by the model (adjusted R^2) was 34%. Birth weight percentile for gestational age was a less significant predictor for PDI and MDI scores than raw birth weight.

Early intervention in the first year of life was not included in our original multivariable models, because it was considered to be a correlate of adverse outcome. However, the percentage of subjects who received early intervention varied significantly by center, ranging from 0% to 23% ($P=0.02$) for early intervention administered for the indication of a cognitive disorder and from 0% to 78% for receipt of any form of early intervention (eg, physical therapy, occupational therapy). We therefore explored whether center differences in the percentages of children receiving either early intervention for a cognitive disorder or any form of early intervention in the first year of life could explain the center effect on outcomes. Mean PDI and MDI scores were significantly lower on average by 11 points in those who received early intervention for a cognitive disorder in comparison with those who did not (PDI, 66.4±18.0 versus 75.5±19.3, $P=0.014$; MDI, 78.7±20.7 versus 90.1±17.0, $P<0.001$). Similarly, children who received any form of early intervention in the first year of life (eg, physical therapy, occupational therapy) fared worse than those who received no form of early intervention (PDI, 67.8±18.3 versus 81.5±17.9, $P<0.001$; MDI, 84.1±19.0 versus 93.9±14.7, $P<0.001$). However, adjustment for either of these intervention terms in the final multivariable models for MDI and PDI did not appreciably alter the effects of center on developmental scores. Similarly, we could find no other center characteristics, such as center volume or surgeon volume, that had a significant effect on PDI or MDI score in multivariable analysis. Finally, we explored whether the center effect could be related to an outlier; when eliminating centers one at a time from the multivariable models, study inferences were similar.

Some variables that had been hypothesized to predict developmental outcome were notable for their lack of association with either PDI or MDI scores. Perfusion type examined both as a categorical variable (DHCA, RCP, or DHCA together with RCP), and as total minutes of DHCA during Norwood surgery was not associated with PDI score in univariate analyses. MDI scores differed ($P<0.001$) in univariate analysis among patients who underwent vital organ support during the Norwood procedure using DHCA, RCP, or a combination of DHCA and RCP (mean scores 85.1, 93.4, and 92.0, respectively, $P<0.001$). As noted above, perfusion type was not an independent predictor of MDI in multivariable analysis. Because the final multivariable model included clinical center, we further explored whether perfusion type would become an independent predictor of MDI if site were not considered. Even then, perfusion strategy did not meet the

Table 1. Univariate Regressions Using Predictors From Birth to Norwood Preoperative Period

		Bayley PDI Score		Bayley MDI Score	
Variable	Mean±SD or %	Slope or Mean	*P* Value	Slope or Mean	*P* Value
Site			0.006		<0.001
Birth					
Gestational age, wk	38.4±1.4	1.00	0.19	1.52	0.03
Gestational age<37 wk			0.03		0.06
Yes	7.3	65.9		82.0	
No	92.7	75.1		89.2	
Birth weight, g	3157±512	0.005	0.01	0.008	<0.001
Birth weight percentile for gestational age	38.3±27.3	0.07	0.07	0.11	0.004
Birth weight <2500 g			0.01		0.006
Yes	9.2	65.6		80.2	
No	90.8	75.3		89.6	
Pre-Norwood HC-for-age *z*	−0.6±1.4	1.09	0.19	2.29	0.002
Multiple birth					
Yes	3.8	61.2	0.02	78.4	0.04
No	96.2	96.2		89.1	
Demographics					
Maternal education			0.03		<0.001
Elementary	3	66.1		70.7	
Junior high	2	52.8		61.6	
Partial high	8	79.2		89.7	
Graduate high	19	73.0		88.4	
Partial college	30	72.6		88.5	
College graduate	27	77.7		90.8	
Postgraduate	11	76.9		92.4	
Genetic and other anomalies					
Genetic syndrome			0.004		<0.001
Yes	3.8	58.2		65.3	
No	77.4	75.9		89.9	
Unknown	18.8	71.6		88.6	
Other anomaly			0.002		0.006
Yes	23.2	68.7		83.1	
No	58.3	77.5		90.8	
Unknown	18.5	71.9		89.1	
Preoperative					
Age at Norwood admission, days	1.0±2.3	0.98	0.04	0.93	0.04
Mechanical ventilation			0.11		0.02
Yes	42.2	72.4		86.0	
No	57.8	76.1		90.7	
Pre-Norwood respiratory failure			0.11		0.03
Yes	10.9	69.5		82.6	
No	89.1	75.0		89.4	
Pre-Norwood metabolic acidosis			0.90		0.05
Yes	5.4	73.9		80.4	
No	94.6	74.5		89.2	
Cardiac catheterization intervention			0.45		0.02
Yes	4.5	70.6		77.6	
No	95.5	74.6		89.2	

(*Continued*)

Table 1. Continued

Variable	Mean±SD or %	Bayley PDI Score		Bayley MDI Score	
		Slope or Mean	*P* Value	Slope or Mean	*P* Value
No. of complications			0.51		0.002
0	77.4	75.0		90.2	
1	14.0	71.3		80.3	
≥2	8.6	74.3		88.3	

Birth weight percentile for gestational age could be calculated for gestational ages between 35 and 41 weeks. Because 8 subjects were born at <35 weeks and 1 subject was born at 42 weeks, the percentile for birth weight for gestational age was set to missing for 9 subjects. Factors with $P<0.05$ for either the PDI or MDI score are shown. HC indicates head circumference; *z*, *z* score; PDI, Psychomotor Development Index; and MDI, Mental Development Index.

criteria for inclusion because of low reliability by bootstrapping (40%). In addition, we found no significant relationship of PDI or MDI score to other aspects of vital organ support, such as hematocrit or pH strategy during core cooling or to patient factors such as diameter of the ascending aorta or cardiac anatomy.

Finally, we assessed whether the strength of the candidate predictors varied according to 4 prespecified patient factors (see Methods) related to birth weight, preterm status, pre-Norwood head circumference *z* score, and presence of a genetic syndrome or other anomalies. The lack of effect of shunt type on PDI and MDI scores was consistent across the predetermined subgroups. The association of other candidate predictors with outcome also did not vary according to these prespecified patient factors. None of the interaction terms entered the final multivariable models for either MDI or PDI.

Discussion

We found a high prevalence of neurodevelopmental impairment in patients with HLHS syndrome and other single right ventricle anomalies, discouragingly similar to that described in patients who underwent Norwood surgery from 1998 to 2003.[5] Lower BSID-II scores at age 14 months were predicted by both innate patient factors and measures of greater severity of illness. Patient factors that portended greater risk included the presence of genetic syndromes or other anomalies, lower maternal education, and lower birth weight. Consistent with previous reports,[23,24] patients in our study with a more complicated postoperative course following the Norwood procedure also had worse outcomes, as indicated by independent risk factors of longer postoperative mechanical ventilation or hospital stay. These measures of longer recovery likely integrate the effects of many other factors during the Norwood hospitalization, including adverse events, low cardiac output, poor feeding, or comorbidities. Between Norwood discharge and age 12 months, a greater number of complications were also associated with worse development, a novel finding that highlights ongoing brain vulnerability and opportunities for intervention. Subjects whose Norwood procedure was performed with the use of the recently popularized RV-to-PA shunt scored no better on the BSID-II than those receiving a MBT shunt, even though they had better early survival.[25] Thus, patient characteristics and indices of greater severity of illness were more highly associated with later neurodevelopmental outcome than specific operative management strategies.

Methods of vital organ support during infant heart surgery are among the best studied and most easily modified potential risk factors for brain injury. Previous studies have suggested that longer duration of DHCA may have adverse effects on neurodevelopmental outcomes.[2,29] An alternative to DHCA, RCP involves low-flow perfusion to the brain during aortic arch reconstruction and has been hypothesized to be potentially neuroprotective relative to DHCA. A single-center randomized trial comparing DHCA with RCP during Norwood surgery found no evidence that RCP improves infant development at age 1 year.[30] Nonetheless, half of surgeons who responded to a survey on support techniques recently reported routine or exclusive use of RCP.[31] In our study, neither longer DHCA duration nor use of a predominant DHCA strategy during the Norwood procedure emerged as an independent risk factor for any developmental outcome. No other perfusion techniques used during cardiopulmonary bypass emerged as independent risk factors for worse developmental outcomes despite a wide range of practices among participating centers.

Most patient factors are not modifiable, but birth weight might be improved by postponing the time of elective delivery to 39 to 40 weeks, as recommended by the American College of Obstetricians and Gynecologists.[32,33] In a recent large series, 26% of neonates with critical congenital heart disease were delivered electively at 37 to 38 weeks gestation,[34] a percentage that is similar to national statistics.[32]

The modest percentage of variance in outcomes explained by postnatal factors in our study is consistent with growing evidence that risk for adverse neurodevelopmental outcomes begins prenatally. Patients with HLHS have a high rate of cerebral dysgenesis and microcephaly,[8,35] suggesting that genetic factors and epigenetic insults contribute to abnormalities in brain development.[12] Furthermore, abnormal fetal cerebral hemodynamics could adversely affect brain development. In comparison with normal third-trimester fetuses, those with HLHS and other congenital heart lesions have progressively smaller gestational age- and weight-adjusted brain volume, as well as perturbed neuroaxonal development and metabolism on

Table 2. Univariate Regressions Using Predictors From Norwood Operation to 14 Months

		Bayley PDI score		Bayley MDI Score	
Variable	Mean±SD or %	Slope or Mean	*P* Value	Slope or Mean	*P* Value
Stage 1 Surgery					
Perfusion type			0.70		<0.001
DHCA only	52.6	73.7		85.0	
RCP with DHCA ≤10 min	26.9	75.0		93.4	
RCP and DHCA	20.5	76.1		92.3	
DHCA time, min	29.8±22.1	−0.04	0.47	−0.16	<0.001
RCP time, min	24.6±29.6	0.01	0.73	0.11	0.001
α-stat vs pH-stat during cooling			0.52		0.04
PH-stat	75.5	74.0		89.8	
α-stat	24.5	75.7		85.2	
Hematocrit, %	30.1±5.1	−0.50	0.02	−0.20	0.31
Open sternum					
Yes	75.2	72.7	0.005	87.6	0.06
No	24.8	79.7		91.9	
α-Blockade					
Yes	48.7	76.3	0.10	91.6	0.004
No	51.3	72.7		85.9	
Post-Norwood to Norwood hospital discharge					
CPR					
Yes	7.0	68.6	0.16	80.5	0.02
No	93.0	74.8		89.3	
ECMO					
Yes	4.1	66.5	0.15	78.7	0.04
No	95.9	74.7		89.1	
No. of cardiac surgeries	1.4±1.3	−3.67	<0.001	−3.11	<0.001
No. of complications	2.2±2.6	−1.97	<0.001	−1.75	<0.001
Duration of ventilation, days	10.4±21.3	−0.18	0.001	−0.22	<0.001
Postoperative LOS, days	32.4±30.1	−0.22	<0.001	−0.18	<0.001
Norwood discharge to age 12 mo					
Stage II surgery LOS, days	13.1±16.5	−0.42	<0.001	−0.29	<0.001
No. of complications	2.4±2.5	−2.07	<0.001	−2.13	<0.001
No. of cardiac catheterization interventions	0.7±1.2	−2.17	0.014	−0.93	0.25
From Norwood to age 12 mo					
No. of episodes of DHCA (linear fit)	1.0±0.7	−1.14	0.48	−4.41	0.002
No. of episodes of DHCA			0.74		0.006
0	25.2	75.2		93.8	
1	53.8	74.8		87.6	
2	21.0	72.8		85.2	
Cumulative duration of DHCA, min	37.3±29.7	−0.05	0.22	−0.13	<0.001
No. of SAEs (linear fit)	0.2±0.5	−7.51	<0.001	−6.75	<0.001
No. of SAEs			0.002		0.002
0	78.7	76.4		90.5	
1	18.2	67.7		81.9	
≥2	3.2	63.7		82.2	
Somatic growth pre-stage II minus pre-Norwood					
Weight-for-age *z*	−1.4±1.1	2.49	0.01	−0.04	0.96
HC-for-age *z*	−0.9±1.7	2.69	<0.001	2.06	0.001

(*Continued*)

Table 2. Continued

Variable	Mean±SD or %	Bayley PDI score		Bayley MDI Score	
		Slope or Mean	*P* Value	Slope or Mean	*P* Value
Month 14 minus pre-Norwood					
Weight-for-age *z*	−0.3±1.3	1.73	0.04	−0.15	0.84
Height-for-age *z*	−0.9±1.7	1.27	0.05	0.26	0.65
Month 14 minus pre-stage II					
HC-for-age *z*	1.2±1.6	−2.32	0.001	−1.86	0.004

Factors with $P<0.05$ for either the PDI or MDI score are shown. HC indicates head circumference; LOS, length of stay; *z*, *z* score; DHCA, deep hypothermic circulatory arrest; RCP, regional cerebral perfusion; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; SAE, serious adverse event; PDI, Psychomotor Development Index; and MDI, Mental Development Index.

fetal brain magnetic resonance imaging.[9] On histopathologic examination, the HLHS fetus already has chronic diffuse white matter injury.[12] Preoperatively, abnormalities of brain metabolism and microstructure, suggestive of brain immaturity, are present in a high percentage of infants with single-ventricle lesions and D-transposition of the great arteries.[36] Indeed, brain maturation in neonates with HLHS and D-transposition of the great arteries is delayed by ≈1 month in comparison with a normative sample.[11] Moreover, Andropoulos et al[10] showed that low brain maturity score by magnetic resonance imaging is associated with greater brain injury in both the preoperative and postoperative periods. Thus, preoperative condition could increase brain vulnerability to perioperative hemodynamic instability and intraoperative hypoxia-ischemic injury.

Table 3. Multivariable Regression Models for Bayley Summary Scores

	Estimate	Covariate-Adjusted Mean	*P* Value	Partial R^2, %	Multivariable Bootstrapping Reliability, %
PDI score multivariable model (N=313, adjusted R^2=0.26)					
Site			0.003	10	55
Low birth weight (<2500 g)			0.02	2	80
Yes	−7.70	69.5			
No	Ref	77.2			
Log length of Norwood hospitalization, days	−11.53		<0.001	13	77
No. of complications post-Norwood discharge up to 12 mo	−1.60		<0.001	5	85
MDI score multivariable model (N=311, adjusted R^2 =0.34)					
Site			<0.001	13	68
Low birth weight			0.04	2	66
Yes	−6.16	81.8			
No	Ref	88.0			
Genetic syndrome and/other anomalies			0.04	2	53
Yes	−7.19	80.9			
No	−2.25	85.8			
Unknown	Ref	88.1			
Maternal education level			0.045	4	70
Elementary	−14.51	77.2			
Junior high	−21.60	70.1			
Partial high	−2.49	89.2			
Graduate high	−3.93	87.8			
Partial college	−3.02	88.7			
College graduate	−1.97	89.7			
Post graduate	Ref	91.7			
Log days of ventilator post-Norwood during hospitalization	−7.48		<0.001	10	59
No. of complications post-Norwood discharge up to 12 mo	−1.47		<0.001	5	78

Model selection rule required $P<0.05$ for all terms in the model and a reliability estimate of >50%. Ref indicates reference group; PDI, Psychomotor Development Index; and MDI, Mental Development Index.

The results of this study must be viewed in light of its limitations. We are uncertain why the clinical center at which the Norwood procedure was performed emerged as an independent predictor of both PDI and MDI scores in final multivariable models. We prospectively recorded data on many potential risk factors, including details of perfusion techniques. Nonetheless, it is possible that differences in developmental scores according to site reflect residual confounding from unmeasured variables in patient characteristics or perioperative management. For example, neurotoxicity of anesthetic agents in the developing brain has been an area of increasing concern, but the types and quantities of anesthesia were not recorded in the SVR trial.[37–39] It is also possible that differences in site scores were related to subjective differences in psychologist's scoring at the centers. However, the test administration technique of all psychologists was standardized centrally before their testing of study subjects, and there was drift in scores over time at only 1 site. Furthermore, study inferences were similar when centers were eliminated from the multivariable models one at a time. Of note, the examiners were blinded to treatment group, and shunt types were balanced within surgeon and thus, within clinical center, so that the treatment group comparison should not be biased.

We performed developmental testing at the oldest possible age within the design of the SVR trial, for which 14-month development was a secondary outcome. It is difficult to assess developmental skills such as visual perception, perceptual-motor integration, early number concepts, or prewriting skills before age 2 years. Bayley scores at 14 months are poorly predictive of later neurodevelopment in normally developing children, but their predictive validity is better in samples of at-risk infants,[40] including children with congenital heart disease.[41] The specificity and negative predictive value of low scores for later cognitive function are relatively high[41,42]; children who score well in infancy tend to score well later on. However, sensitivity and positive predictive value tend to be lower, indicating that only a subset of children who score poorly in infancy will score poorly later on. This may reflect many factors, including the benefits of early intervention and the influence of intercurrent medical and psychosocial events. Poor PDI scores are, however, predictive of later motor function, with strong tracking of motor proficiency from the 18-month PDI score to the prepubertal period.[43] Furthermore, the Bayley Scales at 14 months have good concurrent validity and reliability; because assessment of infants with congenital heart disease has commonly been performed using the Bayley Scales at age 1 year, its use in the current study allows comparison with previously published data.

We were unable to perform brain magnetic resonance imaging on study subjects because this would have required general anesthesia in medically fragile children, posing a controversial risk-to-benefit ratio. Neurological examination also was not incorporated in the study protocol and would have been challenging to standardize among 15 centers. Many variables were highly associated with each other. We did not adjust for multiple comparisons in our analyses. However, the probability values for the predictors in the final models were highly statistically significant. We used bootstrapping to assess the reliability of variables that were selected in our multivariable models, providing reassurance about their robustness. Intraoperative variables did not emerge as independent predictors of neurodevelopmental outcomes, but adjustment for postoperative events in the causal pathway may have diminished their statistical significance. Finally, our study design allowed us to identify many of the variables associated with adverse neurodevelopmental outcome, but not to determine causality.

In summary, in the largest multicenter prospective study to date of children with HLHS and other single right ventricle anomalies undergoing staged reconstruction, we found that neurodevelopmental impairment was most highly associated with innate patient factors and general medical morbidity in the first year of life. Substantial improvement in neurodevelopmental outcome in this vulnerable population is likely to require interventions that occur outside the operating room, such as discouraging elective deliveries before 39 weeks, protecting the brain during preoperative and postoperative hemodynamic instability, and optimizing developmental support after Norwood discharge. Although single ventricle lesions and their management are unusually complex, they constitute an important model for considering universal effects of critical congenital defects (both cardiac and noncardiac) requiring complex interventions in the newborn period.[38]

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See online-only Data Supplement Materials for a complete list of the Pediatric Heart Network Investigators.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Survival to adulthood is becoming a reality for patients with hypoplastic left heart syndrome and related single right ventricle anomalies treated with staged palliation from the Norwood operation to the Fontan procedure. We assessed neurodevelopment at age 14 months in the 15-center, randomized Single Ventricle Reconstruction trial by using the Psychomotor Development Index and Mental Development Index of the Bayley Scales of Infant Development-Second Edition. We found a high prevalence of neurodevelopmental impairment in patients with hypoplastic left heart syndrome and related single right ventricle anomalies. Lower Bayley Scales of Infant Development-Second Edition scores at age 14 months were predicted by both innate patient factors and measures of greater severity of illness. Patient factors that portended greater risk included the presence of genetic syndromes or other anomalies, lower maternal education, and lower birth weight. Patients with a more complicated postoperative course following the Norwood procedure also had worse outcomes, as indicated by independent risk factors of longer postoperative mechanical ventilation or hospital stay. Between Norwood discharge and age 12 months, a greater number of complications were also associated with worse development, a novel finding that highlights ongoing brain vulnerability and opportunities for intervention. Neither the type of systemic-to-pulmonary-artery shunt nor bypass-related variables were predictors of Bayley Scales of Infant Development-Second Edition scores in multivariable analyses. Thus, patient characteristics and indices of greater severity of illness were the factors most highly associated with later neurodevelopmental outcome. Substantial improvement in neurodevelopmental outcome in this vulnerable population is thus likely to require inclusion of interventions that occur outside the operating room.

Early Developmental Outcome in Children With Hypoplastic Left Heart Syndrome and Related Anomalies: The Single Ventricle Reconstruction Trial

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Supplemental Material

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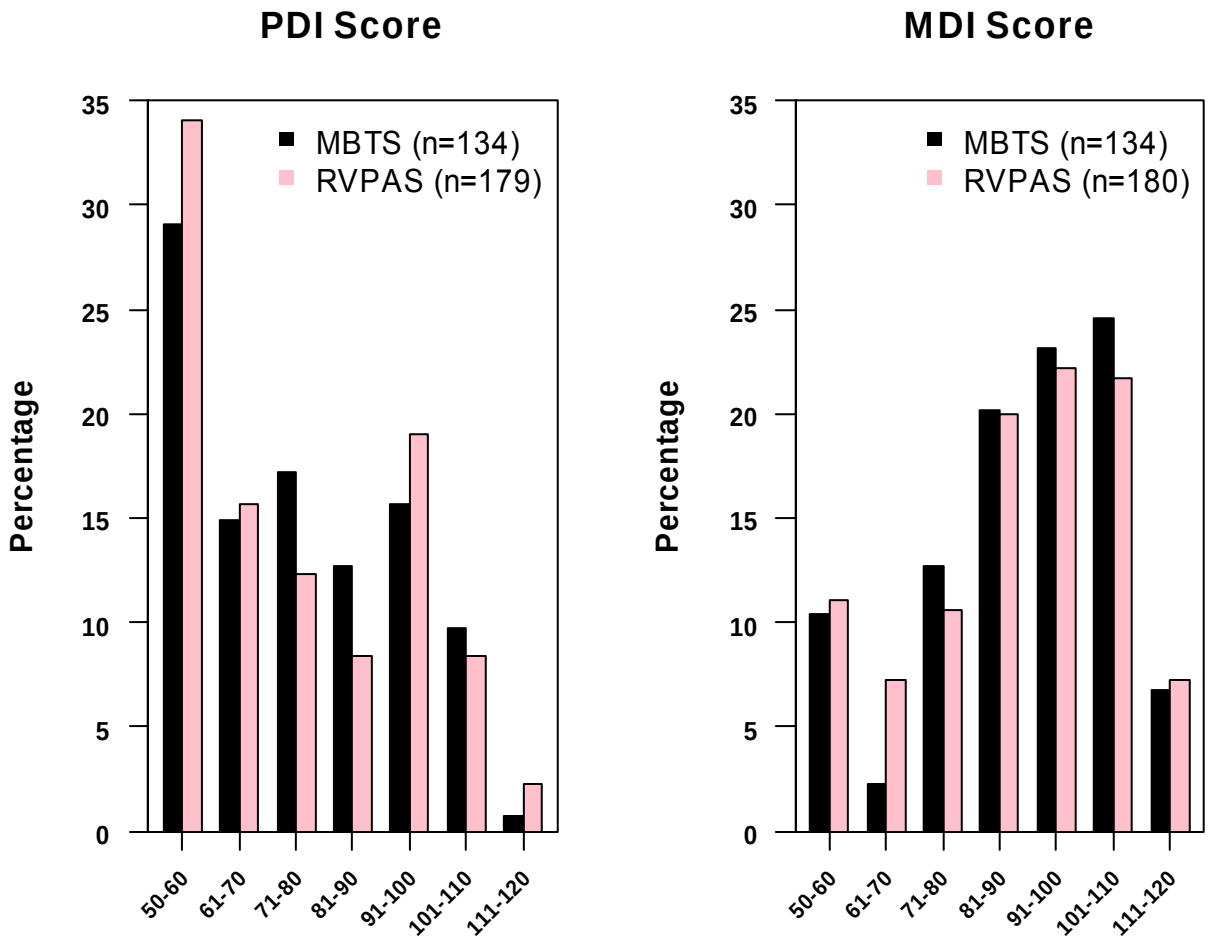
Supplemental Figure 1



Supplemental Figure 1 Legend

Histogram depicting the number of subjects according to shunt type and scores on the Psychomotor Development Index (PDI, left panel) and Mental Development Index (MDI, right panel) of the Bayley Scales of Infant Development®—Second Edition. MBTS = Modified Blalock-Taussig Shunt. RVPAS = right-ventricular-to pulmonary-artery shunt.

Supplemental Table 1. Candidate Variable List for Modeling of Neurodevelopmental Outcomes

Site and Surgeon	
Site	Surgeon Norwood volume (4 levels)
Prenatal	
Prenatal Diagnosis	Fetal intervention
Birth	
Birth weight, g	Gestational age, wk
Birth weight <2500 g	Gestational age <37 wk
Apgar score at 1 min	Birth weight percentile for gestational age
Apgar score at 5 min	Multiple birth
Demographic	
Gender	Race (white vs. black vs. other)
SES score (U.S. Census-based)	Hispanic ethnicity
% below federal poverty level	Highest maternal education level (7 levels)
Hollingshead Score	Caregiver education level (5 levels)
Anatomy	
Hypoplastic left heart syndrome	Obstructed pulmonary venous return
Aortic atresia	Ascending aorta diameter, mm
Genetic and other anomalies	
Genetic syndrome	Other anomaly

Genetic syndrome or anomaly

Pre-operative

Head circumference-for-age z-score	Head circumference-for-age z-score <-1
Highest lactate level, mmol/l	Age at Norwood admission, days
Mechanical ventilation	Cardiac catheterization intervention
Ventilation for metabolic acidosis	Cardiac surgery
Ventilation for apnea	Number of complications (linear fit)
Ventilation for shock	Number of complications (0 vs. 1 vs. ≥2
Ventilation for respiratory failure	Pre-operative length of stay, days [5]
Pre-Norwood intubation for shock or metabolic acidosis; or highest lactate >5 mmol/L	

Stage 1 Surgery

Age at Norwood, days	Alpha-stat vs. pH-stat during cooling:
Shunt at end of operation (MBTS vs. RV-to-PA)	Alpha-stat vs. pH-stat during warming
Perfusion type (DHCA vs. RCP vs. DHCA/RCP)*	Lowest neuroprotective temperature during cardiopulmonary bypass, °C
Total support time, min	Aprotinin
DHCA time, min	α-blockade
RCP time, min	ECMO

Lowest hematocrit before initiation of cardiopulmonary bypass, %	
Post Norwood to Norwood hospital discharge	
Open sternum	Surgery requiring bypass
CPR	Number of complications
ECMO	Total duration of ventilation, days
Cardiac catheterization intervention	Post-operative length of stay, days
Number of cardiac surgeries	Shunt at discharge (MBTS vs. RV-to-PA)
Norwood discharge to 12 months	
Stage II hospitalization length of stay, days	Number of complications
Number of cardiac catheterization interventions	
From Norwood to 12 months	
# operations with CP bypass (linear fit)	# Episodes of DHCA (linear fit)
# operations with CP bypass (0 vs. 1 vs. 2. vs. 3 vs. 4)	# Episodes of DHCA (0 vs. 1 vs. 2 vs. 3)
Cumulative interval support time	Number of serious adverse events (linear fit)
Cumulative duration of DHCA, min	Serious adverse events (0 vs. 1 vs. ≥2)

Change in Growth: Month 14 minus Pre Norwood

Weight-for-age z-score	Head circumference-for-age z-score
Height-for-age z-score	Body mass index, kg/m^2

Change in Growth: Month 14 minus Pre Stage II

Weight-for-age z-score	Head circumference-for-age z-score
Height-for-age z-score	Body mass index, kg/m^2

*DHCA classification defined as DHCA for >10 minutes. DHCA=deep hypothermic circulatory arrest; RCP=regional cerebral perfusion

CP=cardiopulmonary

CPR=cardiopulmonary resuscitation

ECMO=extracorporeal membrane oxygenation

MBTS=modified Blalock-Taussig shunt

RV-to-PA=right ventricle to pulmonary artery

SES=socioeconomic